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Effect of the SARS-CoV-2 Vaccination on the Duration of COVID-19 Symptoms in Outpatients in Morocco

Fas'ta Ayakta Tedavi Gören Hastalarda SARS-CoV-2 Aşısının COVID-19 Semptomlarının Süresine Etkisi

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Abstract

Introduction: To identify if there is an association between Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) vaccination and the duration of symptoms in patients with mild-to-moderate Coronavirus disease-2019 (COVID-19).
Materials and Methods: We conducted a prospective observational cohort study which included patients with mild-to-moderate COVID-19 that was confirmed via biological and/or radiological methods (reverse transcription-polymerase chain reaction, TAG-rapid, and chest computed tomography) and who were treated as outpatients from August 2021 to September 2021. The duration of symptoms was defined as the interval between the onset of symptoms and their resolution. We compared the symptom duration between unvaccinated, partially vaccinated, and fully vaccinated patients. The other variables were also adjusted.
Results: We included 283 patients with positive SARS-CoV-2 test results. Among these participants, 28.6% were fully vaccinated, 25.1% were partially vaccinated, and 46.3% were unvaccinated. The median duration of symptoms was 10 days, interquartile range [(IQR) (7-13)] in vaccinated patients and 13 days [IQR (9-15)] in unvaccinated patients. After adjusting for confounding factors, a short duration of symptoms was significantly associated with age <50 years [odds ratio (OR)=0.41; 95%, confidence interval (CI) (0.22-0.76); p<0.005] and the vaccination status. Patients who received one vaccine dose had an OR of 0.48 [95% CI (0.26-0.88); p<0.019]. Patients who received both vaccine doses had an OR of 0.26 [95% CI (0.12-0.50); p<0.000].
Conclusion: There was a significant association between vaccination status against SARS-CoV-2 and short duration of symptoms in outpatients with mild-to-moderate COVID-19. This finding may have significant public health implications like admitting the effective role of vaccination in preserving individual and collective well-being. In addition, it provides insights into vaccination strategies for patient care by giving indications of how long symptoms persist, enabling more effective management of isolation and quarantine measures.
Keywords: SARS-CoV-2, vaccination, duration of symptoms, moderate forms

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Öz

Giriş: Hafif-orta şiddette Koronavirüs hastalığı-2019 (COVID-19) hastalarında Şiddetli akut solunum yolu sendromu-Koronavirüs-2 (SARS-CoV-2) aşısı ile semptomların süresi arasında bir ilişki olup olmadığını belirlemektir.
Gereç ve Yöntem: Biyolojik ve/veya radyolojik yöntemlerle (ters transkripsiyon-polimeraz zincir reaksiyonu, TAG-rapid ve göğüs bilgisayarlı tomografi) doğrulanan ve Ağustos 2021'den Eylül 2021'e kadar ayakta tedavi gören hafif-orta şiddette COVID-19'lu hastaları içeren prospektif gözlemsel bir kohort çalışması gerçekleştirilmiştir. Semptomların süresi, semptomların başlangıcı ile düzelmesi arasındaki süre olarak tanımlandı. Aşılanmamış, kısmen aşılanmış ve tamamen aşılanmış hastaları semptom süresi açısından karşılaştırdık. Diğer değişkenler de düzeltildi.
Bulgular: SARS-CoV-2 testi pozitif olan 283 hasta dahil edilmiştir. Bu hastaların %28,6'sı tam aşılı, %25,1'i kısmen aşılı ve %46,3'ü aşısızdı. Aşılanmış hastalarda ortalama semptom süresi 10 gün olup, çeyrekler arası aralık (IQR) 7-13 idi ve aşılanmamış hastalarda 13 gün olup IQR 9-15 idi. Sonuçları etkileyebilecek diğer faktörler düzeltildikten sonra, semptomların kısa süreli olması, <50 yaş olmak [olasılık oranı (OR)=0,41; %95, güven aralığı (CI) (0,22-0,76); p<0,005] ve aşılanma durumuyla önemli ölçüde ilişkiliydi. Tek doz aşılanan hastaların OR'si 0,48 idi [%95 GA (0,26-0,88); p<0,019]. İki doz aşılanan hastaların OR'si 0,26 idi [%95 GA (0,12-0,50); p<0,000].
Sonuç: Hafif-orta şiddette COVID-19'lu hastalarda SARS-CoV-2'ye karşı aşılanma durumu ile semptomların kısa süresi arasında anlamlı bir ilişki vardı. Bu bulgunun, aşılamanın bireysel ve kolektif refahın korunmasındaki etkili rolünün kabul edilmesi gibi önemli halk sağlığı sonuçları olabilir. Ayrıca semptomların ne kadar süre devam ettiğine dair göstergeler vererek hasta bakımına yönelik aşılama stratejileri hakkında bilgi sağlar ve izolasyon ve karantina önlemlerinin daha etkili bir yönetimine olanak tanır.
Anahtar Kelimeler: SARS-CoV-2, aşılama, semptomların süresi, orta formlar

Introduction

Vaccination is one of the most important public health interventions to prevent morbidity and mortality[1]. To fight against the Coronavirus disease-2019 (COVID-19), there was a worldwide struggle to find effective vaccines. Since then, several vaccines have been tested and analyzed in clinical trials[2]. Morocco was one of the first countries to implement a vaccination program against the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) on January 28, 2021[3]. Great efforts were made to better manage the disease progression, and 66.41% of the population was vaccinated[3]. In several cases, the anti-COVID-19 vaccination is effective in minimizing the occurrence of a new disease, with the effect being greatest after two vaccinations[4]. The mild and moderate forms of COVID-19 are commonly seen; however, all the epidemiological studies have focused on the severe form of the disease[5]. Studies should highlight the additional effects of vaccination on the most common form of this emerging infection[6]. In this study, we aimed to determine if there were any indirect benefits of the COVID-19 vaccination in vaccinated outpatients with mild to moderate form of the disease. We hypothesized that the COVID-19 vaccination minimizes and reduces the duration of symptoms, which could impact the population on a social, economic, and professional level.

Materials and Methods

Study Design and Participants

Between August and September 2021, Morocco experienced an increase in the number of COVID-19 cases, with the center receiving approximately 200 cases per day. We randomly drew 400 patient files to be included in the study by stratifying according to days. Subsequently, we excluded patient files where the date of onset of symptoms was not mentioned. The included patients were followed up by phone for a month. The duration of symptoms was measured as the time between the onset of symptoms to its clearance. During the study period, when the SARS-CoV-2 vaccination was newly introduced in Morocco, the vaccination status the study participants were as follows: fully vaccinated, individuals who had received both the vaccine doses; partially vaccinated, individuals who had received a single dose; and unvaccinated, individuals who had not received the vaccine.

The Ethics Committee of the University Hospital of Fez granted approval for the study (no: 03/21, date of approval: 11.02.2021). Prior to enrollment, all participants were provided with an explanation of the study's objectives, and they gave their informed consent.

Inclusion criteria: Outpatients aged >18 years who were confirmed to have mild-to-moderate COVID-19 via biological and/or radiological modalities [e.g., reverse transcription-polymerase chain reaction (RT-PCR), TAG-rapid, and thoracic computed tomography] were included in the study. The mild-to-moderate form was defined based on the oxygen saturation (SpO_2 ≥94%) and clinical examination and imaging findings, such as signs of lower respiratory tract. Additionally, patients with any of the signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, and muscle pain) without breathlessness, dyspnea, or abnormalities on chest imaging were included in the study[7].

Exclusion criteria: Patients who did not consent to participate in the study and/or did not fulfill the inclusion criteria were excluded from the study.

Data Collection

Data was collected by a medical team involved in the study. For data entry and data quality control, the web application Research Electronic Data Capture "REDCap"(Developed by Vanderbilt University, Nashville, Tennessee, USA) was used[8].

The data collection form included the following parameters:

Socio-demographic variables: Age and sex.

Clinical data:

- Comorbidities and current onset symptoms.

- SARS-CoV-2 infection status (confirmed using RT-PCR, TAG-rapid, and chest CT).

- Oxygen saturation.

- Heart rate.

- Physical and functional signs.

- Vaccination status and vaccines.

- Treatment.

- Side effects of treatment.

Follow-up information: Date of symptom resolution and disease issue.

Variable treatment: The vaccination status was determined as unvaccinated, partially, or fully vaccinated patients. The duration of symptoms was dichotomous (symptoms lasting <10 days or >10 days). Additionally, we used two age categories (<50 years and 350 years).

Statistical Analysis

All analyses were performed using IBM Statistical Package for the Social Sciences version 21 (IBM Corp., Armonk, NY, USA). Among the descriptive statistics, the continuous variables were reported as means (standard deviations) and medians (interquartile range [IQR]), and the categorical variables were expressed as frequencies and percentages. The medians of the symptom duration according to the vaccination status were compared using the Kruskal-Wallis test after verifying the normality of the distribution. Furthermore, we compared this variable in its categorical form using the chi-square test. A p value of <0.05 was statistically significant. We also performed a univariate analysis to determine whether there was a difference in the treatments administered to the patients according to their vaccination status. A binary logistic regression model was used to adjust for confounding factors. The odds ratio (OR) was calculated as an estimate of the relative risk for presenting the results.

Results

Patient Characteristics

A total of 283 patients were enrolled in the study with a mean age of 37 (18-74) years. Approximately 55.5% of the enrolled participants were female. Among all the participants, 28.6% were fully vaccinated, 25.1% were partially vaccinated, and 46.3% were unvaccinated. Approximately 77.6% of the participants were vaccinated with BBIBP-CorV (China National Pharmaceutical Group (Sinopharm)

No.100, Jinmao Road, Shanghai, China)[9], 21.7% with ChAdOx1 nCoV-19 (AstraZeneca, United Kingdom)[10], and one patient with Ad26COV2. S (Janssen Pharmaceutica and Beth Israel Deaconess Medical Center)[11]. A total of 110 patients (38.9%) had at least one risk factor, with the most common being diabetes (4.2%), hypertension (3.9%), obesity (body mass index ≥30; 13.4%), and smoking (7.4%) (Table 1). All the patients enrolled in this study were symptomatic, with the most commonly symptoms reported being fever (65%), headache (55.5%), anosmia (53.4%), cough (48.1%), and fatigue (43.1%).

The median duration of symptoms was 10 days (IQR, 7-13) in partially or fully vaccinated patients and 13 days (IQR, 9-15) in unvaccinated patients.

Most patients had been administered medications according to the protocol recommended by the Ministry of Health including chloroquine, azithromycin, vitamin C, zinc, and vitamin D. Other treatments were prescribed according to the patient's condition

Table 1. Patient characteristics

Characteristics	n (median or %) (n=283)
Age, median (IQR)	34 (27-46)
BMI, median (IQR)	25 (22-27)
O_2 saturation, median (IQR)	98 (97-99)
Heart rate, median (IQR)	87 (77-99)
Symptom duration, median (IQR)	10 (07-15)
Male sex, n (%)	126 (44.5%)
Risk factors, n (%)	
Any risk factor	110 (38.9%)
Age ≥50	59 (20.8%)
Obesity	38 (13.4%)
Smoking	21 (07.4%)
Diabetes	12 (04.2%)
Hypertension	11 (03.9%)
Vaccination status, n (%)	
Completely vaccinated	81 (28.6%)
Partially vaccinated	71 (25.1%)
Unvaccinated	131 (46.3%)

IQR: Interquartile range, BMI: Body mass index, O_2: Oxygen saturation

and risk factors, including low molecular weight (LMWH) heparin, proton pump inhibitor, other antibiotics, and probiotics (Table 2).

There was no statistically significant difference between the groups. We also examined the relationship between the treatment administered to the patients and the duration of symptoms. The symptoms lasted longer in patients treated with LMWH than in those not treated with LMWH (p<0.003) (Table 2).

A total of 178 patients (64%) had not received any treatment before the consultation; another 100 patients (36%) self-medicated with the COVID-19 medical protocol medications before visiting the hospital. In our cohort 278 (98.2%) patients had a favorable evolution, and the remaining patients had complications. There were no deaths. Approximately 29.8% of the patients developed side effects from the treatment, with the most common being diarrhea (n=67; 23.7%).

Clinical Outcomes According to the Vaccination Status

The univariate analysis to identify an association between risk factors and duration of symptoms revealed that age (p<0.016) and sex (p<0.048) were significant factors. There was no significant association between symptom duration and the other risk factors, such as Hypertension (p=0.064), obesity (p=0.126), and smoking (p=0.314). Additionally, we compared the three groups (fully vaccinated, partially vaccinated, and unvaccinated) to determine whether vaccination status was associated with the symptoms reported by the patients (Table 3). Ageusia was the most common symptom in nonvaccinated patients, while arthralgia, and myalgia were the most common symptoms in vaccinated patients.

Table 2. Association between the treatment and symptom duration

	All patients	Duration of symptoms <10 days	Duration of symptoms >10 days	p value*
Treatment	n (%) (n=283)	n (%) (n=159)	n (%) (n=124)	
Azithromycin	267 (94.3%)	150 (56.2%)	117 (43.8%)	0.99
Chloroquine	3 (01.1%)	2 (66.7%)	1 (33.3%)	1
Vitamin C	275 (97.2%)	153 (55.6%)	122 (44.4%)	0.47
Zinc	269 (95.1%)	150 (55.8%)	119 (44.2%)	0.53
Vitamin D	275 (97.2%)	154 (56.0%)	121 (44.0%)	1
LMWH	34 (12.0%)	11 (32.4%)	23 (67.6%)	**0.003**
Other treatments	47 (16.6%)	26 (55.3%)	21 (44.7%)	0.89
PPI	24 (08.5%)	14 (58.3%)	10 (41.7%)	-
Probiotics	6 (02.1%)	4 (66.7%)	2 (33.3%)	-
Anti-histamines	3 (01.1%)	2 (66.7%)	1 (33.3%)	-
Anti-aggregates	4 (01.4%)	3 (75.0%)	1 (25.0%)	-
Amoxicillin and clavulanic acid	3 (01.1%)	2 (66.7%)	1 (33.3%)	-
Other antibiotics	7 (02.5%)	1 (14.3%)	6 (85.7%)	-

*Cells have an expected count of <5.

LMWH: Low molecular weight heparin, PPI: Proton pump inhibitor

Table 3. Association between the vaccination status and disease symptoms

	Fully vaccinated	Partially vaccinated	Unvaccinated	
Symptoms	n (%)	n (%)	n (%)	p value
Anosmia	36 (44.4%)	40 (56.3%)	75 (57.3%)	0.162
Ageusia	21 (25.9%)	31 (43.7%)	57 (43.5%)	<0.022
Fatigue	33 (40.7%)	24 (33.8%)	65 (40.7%)	0.084
Arthralgia	37 (45.7%)	17 (23.9%)	50 (38.2%)	<0.019
Myalgia	33 (40.7%)	13 (18.3%)	41 (31.3%)	<0.011
Fever	47 (58.0%)	47 (66.2%)	90 (68.7%)	0.277
Headache	42 (51.9%)	40 (56.3%)	75 (57.3%)	0.734
Cough	42 (51.9%)	39 (51.9)	55 (42.0%)	0.154
Diarrhea	17 (21.0%)	7 (9.9%)	30 (22.9%)	0.069

Association Between Vaccination Status and Symptoms Duration

There is statistically significant difference in the duration of symptoms among the three vaccination groups (p<0.001). The proportion of patients with symptoms lasting >10 days was 30.9% [95% CI (21.1-42.1)], 36.6% [95% CI (25.5-48.9)], and 55.7% [95% CI (46.8-64.4)] in the vaccinated, partially vaccinated, unvaccinated groups, respectively (Figure 1).

A statistically significant difference was found between the medians of the symptom duration between the three groups (p<0.003).

A multivariate analysis was performed, considering the following risk factors: sex, age, high blood pressure, obesity, smoking, and the use of LMWH. A shorter duration of symptoms was significantly associated with age <50 years [OR=0.51; 95% CI (0.26-0.97; p<0.041)], nonuse of LMWH [OR=0.31; 95% CI (0.13-0.73); p<0.007], and vaccination status with a dose effect. Partially vaccinated patients had an OR of 0.48 [95% CI (0.26-0.88); p<0.018] and fully vaccinated patients had an OR of 0.27 [95% CI (0.14-0.50); p<0.001] (Table 4).

Discussion

In this study, we analyzed the association between vaccination status and recovery time, as assessed by the duration of symptoms, in patients with mild-to-moderate COVID-19.

We found that 69.1%, 63.4%, and 44.3% of the patients in the vaccinated, partially vaccinated, and unvaccinated group had symptoms lasting <10 days. After adjusting for confounding factors, such as age, sex, obesity, smoking, and comorbidities, we determined that the vaccination status and older age were independently and significantly related to a longer duration of symptoms. This association between age and symptom duration can be explained by the fact that older patients have weaker immune systems[12]. Studies have shown that the Influenza vaccine varies in efficacy according to age, imparting reduced protection in the older adults than in the younger individuals[13-15]. However, the preliminary results from a phase 3 SARS-CoV-2 vaccine trial did not demonstrate a comparable distinction, as the vaccine had a similar efficacy in all age groups[16]. Additionally, the nonuse of LMWH shortened

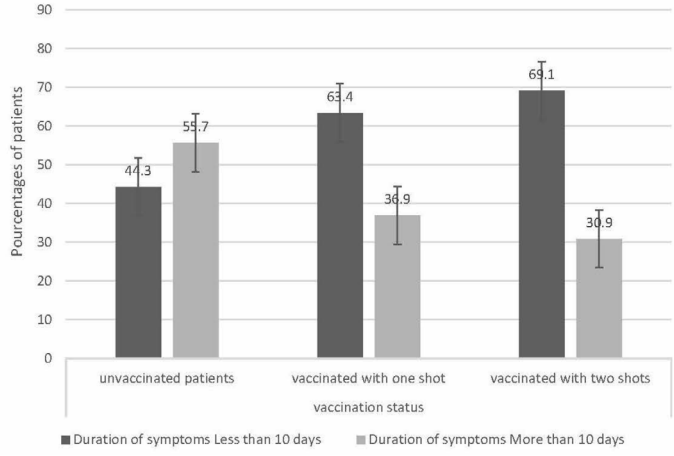

Figure 1. Symptom duration based on the vaccination status

Table 4. Final model of the multivariate analysis

Risk factor	OR (95% CI)	p value
Age range		
Age <50 years	0.510 (0.268-0.973)	<0.041
Age ≥50 years	-	
LMWH use		
LMWH used	0.316 (0.136-0.732)	<0.007
LMWH not used	-	
Vaccination status		
Partially vaccinated (one dose)	0.482 (0.263-0.884)	<0.018
Fully vaccinated (two doses)	0.270 (0.143-0.508)	<0.001
Unvaccinated	-	

LMWH: Low molecular weight heparin, CI: Confidence interval, OR: Odds ratio

the duration of symptoms because patients requiring LMWH needed more time to recover due to their comorbidities[17].

We identified a statistically significant lower incidence of ageusia in vaccinated patients than in unvaccinated patients ($p<0.022$). Conversely, arthralgia ($p<0.019$) and myalgia ($p<0.011$) were more frequently seen in vaccinated patients than in unvaccinated patients. Knight followed up patients with mild COVID-19 until two consecutive confirmatory tests were negative. They found that early symptoms of ageusia were associated with a longer duration of viral shedding[18]. This potentially explains why unvaccinated patients who present with ageusia took longer to recover than those without ageusia. Nevertheless, this symptom is one among several other symptoms that are characteristic of the mild-to-moderate form of COVID-19[7]. Hence, they may not explain the different incidences of these symptoms between vaccinated and unvaccinated patients.

In our study, most patients were vaccinated with BBIBP-CorV. Although we did not evaluate the efficacy of each vaccine, the results of the previous trials have shown that BBIBP-CorV offers sufficient protection against symptomatic and asymptomatic COVID-19 infection[19]. Another UK study evaluated the efficacy of BNT162b2 and ChAdOx1 nCoV-19 against all new SARS-CoV-2 infections with positive PCR tests. The concluded that overall, COVID-19 vaccination reduced the number of new SARS-CoV-2 infections, with no difference between the two vaccines[4]. However, the duration of symptoms for each vaccine type were not been evaluated.

In real life, COVID-19 vaccination strongly impacted the COVID-19-related mortality in Europe and Israel in terms of protection against death, indicating that there is no indirect protection for unvaccinated individuals[20]. Another American study of adults aged ≥50 years with COVID-19 who were treated in ambulatory and inpatient care settings, showed that the vaccines were highly effective against SARS-CoV-2 infections requiring hospitalization[21]. However, real-life studies examining the effect of vaccinations based on symptoms are limited.

Studies indicate that the primary impact of the SARS-CoV-2 vaccine is prevention of COVID-19[22]. Furthermore, it contributes to the mitigation of COVID-19 outbreaks if combined with nonpharmaceutical measures[23]. Vaccination programs may indirectly reduce the risk of infection, either by reducing the number of infected individuals in the population or allowing those are not infected become less infectious. Vaccinated individuals who become infected may have less viral shedding, fewer symptoms, and a more rapid recovery than unvaccinated individuals, which may reduce the risk of transmission to an uninfected person[6].

Ke examined the viral dynamics and infectious viral shedding in a small cohort of SARS-CoV-2-infected adults at different stages of vaccination. They determined that the durations of infectious viral shedding and symptoms were significantly reduced in vaccinated individuals than in unvaccinated individuals[24].

Our results revealed another benefit of COVID-19 vaccines. The reduction of symptom duration may allow an earlier return to work activities in both the formal and informal sectors. Workers in the informal sector represent a large proportion of the Moroccan community[25,26], and the early resolution of symptoms will allow these individuals to return to work earlier with little economic impact on their households. In the formal sector, employees with COVID-19 benefit from a 10-day paid leave. Infection remission will allow them to return to work without having to resort to an extension of the medical leave[27].

Our study has several strengths. It is the only study to have evaluated vaccination and duration of symptoms in ambulatory patients. Its original contribution of the study validates the results of other studies that have evaluated the duration of infection in patients with COVID-19. The data collection in the study was standardized, which limited information bias, and the telephonic follow-up was shortly after the period of illness, which eliminated recall bias.

Study Limitations

Our study had some limitations. First, the recovery time was reported by the patients, which reduced the accuracy of the data. However, this recovery time was measured by the duration of functional symptoms. Second, residual confounding factors cannot be eliminated. Finally, our study was conducted at a single center; thus, the study results may not reflect those of the entire population. So, examining diverse populations across multiple centers could enhance our understanding of the topic. In addition, studying the prolonged effects of the recovery period on patient outcomes through an extended follow-up period could provide a better understanding of the lasting effects of the recovery process. There is also great potential in understanding how psychological and social factors influence recovery time, such as mental health and social support. Further exploring the feasibility of using telemedicine or digital health platforms to monitor recovery progress and provide real-time support to patients is a promising avenue. This approach has the potential to improve both the accuracy of data collection and patient care.

Conclusion

Vaccination provides various benefits to the population by reducing the disease incidence and mortality rate. Additionally, our study showed that vaccination shortens the duration of symptoms in outpatients with mild-to-moderate COVID-19.

Ethics

Ethics Committee Approval: The Ethics Committee of the University Hospital of Fez granted approval for the study (no: 03/21, date of approval: 11.02.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.S., Design: K.S., Data Collection or Processing: K.S., Z.M., F.C., F.B., A.G., Analysis or Interpretation: K.S., Literature Search: K.S., Writing: K.S., A.N.

Conflict of Interest: No conflict of interest was declared by the authors.

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